

We Claim:

1. A process of making 2-butyl-3-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)-
biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one, comprising the step
5 of
reacting 2-butyl-3-(4-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one
with 2-((1-trityl-1H-tetrazol-5-yl))phenylboronic acid in a solvent system
comprising first and second solvents in the presence of a catalyst.
2. The process of claim 1, wherein the catalyst is selected from the group
10 consisting of palladium complexes and a nickel complexes.
3. The process of claim 2, wherein the catalyst comprises a combination of a
palladium complex and a triaryl phosphine.
4. The process of claim 3, wherein the palladium complex is Pd(OAc)₂ and the
triaryl phosphine is triphenyl phosphine.
- 15 5. The process of claim 1, wherein the first solvent is selected from the group
consisting of ethers, formals, hydrocarbons, the tetralins or mixtures thereof.
6. The process of claim 5, wherein the first solvent is selected from the group
consisting of: dimethoxyethane (DME), diethoxymethane (diethyl formal),
tetrahydrofuran, toluene, m-xylene and o-xylene.
- 20 7. The process of claim 6, wherein the first solvent is a mixture of
dimethoxyethane and tetrahydrofuran.
8. The process of claim 7, wherein the ratio of dimethoxyethane to
tetrahydrofuran is about 10:1 to about 1:5 on a volume basis.
9. The process of claim 8, wherein the ratio of dimethoxyethane to
25 tetrahydrofuran is about 6:1 to about 2:1 on a volume basis.
10. The process of claim 1, wherein the second solvent comprises water and an
inorganic base.

11. The process of claim 10, wherein the base is potassium carbonate.
12. The process of claim 1, wherein the reacting is at about reflux for a reaction time of about 2 hours to about 4 hours.
13. A process of making a 3-(haloaryl)-1,3-diazaspiro[4.4]non-1-ene-4-one
5 compound comprising the step of :
combining a 1,3-diazaspiro[4.4]non-1-ene-4-one acid addition salt with a haloaryl compound in a two-phase solvent system comprising first and second solvents, in the presence of a phase transfer catalyst.
14. The process of claim 13, wherein the 1,3-diazaspiro[4.4]non-1-ene-4-one acid
10 addition salt is 2-butyl-1,3-diazaspiro[4.4]-1-ene-4-one hydrochloride and the 3-(haloaryl)-1,3-diazaspiro[4.4]non-1-ene-4-one compound is 2-butyl-3-(4'-bromobenzyl)-1,3- diazaspiro[4.4]non-1-ene-4-one.
15. The process of claim 13, wherein the 1,3-diazaspiro[4.4]non-1-ene-4-one acid addition salt is in combination with salt water and a base.
- 15 16. The process of claim 13, wherein the haloaryl compound is in combination with toluene and a phase transfer catalyst.
17. The process of claim 16, wherein the haloaryl compound is 4 bromobenzyl bromide.
18. The process of claim 15, wherein the inorganic base is KOH.
- 20 19. The process of claim 13, wherein the phase transfer catalyst is selected from the group consisting of quaternary ammonium compounds and phosphonium compounds.
20. The process of claim 19, wherein the phase transfer catalyst is tetrabutylaminonium hydrogensulfate.
- 25 21. The process of claim 13, wherein the combining is at a temperature of from about 20°C to about 95°C.
22. The process of claim 21, wherein the temperature is about 90°C.

23. 2-butyl 1,3- diazaspiro[4.4]non-1-ene-3-(4-bromobenzyl)-4-one prepared according to the process of claim 13.
24. 2-butyl-3-(4-bromobenzyl)-1,3- diazaspiro[4.4]non-1-ene-4-one.
25. A process of making a 5-phenyl-1-trityl-1H-tetrazole compound comprising the steps of reacting 5-phenyl-1H-tetrazole with chlorotriphenylmethane in the presence of a solvent and a base; and recovering 5-phenyl-1-trityl-1H-tetrazole.
26. The process of claim 25, wherein the solvent is tetrahydrofuran and the base is triethylamine.
27. A process of making 2-(1-trityl-1H-tetrazol-5-yl)phenylboronic acid comprising the step of:
reacting 5-phenyl-1-trityl-1H-tetrazole with a borate, in the presence of a solvent and a base.
28. The process of claim 27, wherein the solvent is tetrahydrofuran and the base is butyllithium.
29. The process of claim 27, wherein the reacting is at a temperature not higher than about -20°C.
30. A process of making 2-(1-trityl-1H-tetrazol-5-yl)phenylboronic acid comprising the steps of:
- combining 5-phenyl-1H-tetrazole with chlorotriphenylmethane in the presence of a solvent and a first base;
 - combining the product of step a with a borate, in the presence of a solvent and a second base; and
 - recovering 2-(5-tetrazoyl)phenylboronic acid.
31. The process of claim 30, wherein the solvent is tetrahydrofuran.
32. The process of claim 30 wherein the first base is triethylamine, and the second base is butyllithium.

33. A process for preparing irbesartan comprising the steps of:

- a) providing a solution of 2-butyl-3-[2'-(1-trityl-1H-tetrazol-5-yl)biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one in a solvent;
- b) acidifying the solution;
- 5 c) neutralizing the solution and separating the trityl alcohol, whereby a second solution is obtained
- d) acidifying the second solution;
- e) cooling the acidified second solution; and
- f) recovering irbesartan.

10 34. The process of claim 33, wherein the solvent in step a is acetone.

35. The process of claim 33, wherein the second solution is cooled to about 0°C to about (-4°C).

36. In a process for making irbesartan, step of:

15 reacting 2-butyl-3-(4-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one with 2-(5-(1-trityl-1H-tetrazole))phenylboronic acid in a solvent system comprising first and second solvents in the presence of a catalyst.

37. In a process for making irbesartan, comprising the steps of

20 reacting a 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one acid addition salt with a haloaryl compound in a two-phase solvent system comprising first and second solvents, in the presence of a phase transfer catalyst.

38. In a process for making irbesartan, the step of:

combining 5-phenyl-1H-tetrazole with chlorotriphenylmethane in the presence of a solvent and a base;

25 39. In a process for making irbesartan the step of reacting 5-phenyl-1-trityl-1H-tetrazole with a trialkylborate in the presence of a base.

40. A process for making irbesartan, comprising the steps of:

- a) combining 5-phenyl-1-trityl-1H-tetrazole with a borate, in the presence of a solvent and a base;
- b) recovering 2-(5-tetrazoyl)phenylboronic acid; and
- c) converting the product of step b to irbesartan.

5 41. A process for making irbesartan, comprising the steps of:

- a) combining 5-phenyl-1H-tetrazole with chlorotriphenylmethane in the presence of THF and triethylamine;
- b) combining the product of step a with a borate, in the presence of THF and butyllithium;
- 10 c) recovering 2-(5-tetrazoyl)phenylboronic acid;
- d) combining 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one acid addition salt with a bromobenzyl bromide in a solvent system comprising first and second solvents, wherein the first solvent is a mixture of salt water and KOH, and the second solvent is toluene in admixture
15 with a phase transfer catalyst selected from the group consisting of quaternary ammonium compounds and phosphonium compounds;
- e) separating the two phases obtained;
- f) recovering 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one;
- 20 g) reacting the product recovered in step c with the product recovered in step f in a two-phase solvent system comprising first and second solvents, in the presence of a catalyst, wherein the first solvent is selected from the group consisting of ethers, formals, hydrocarbons, tetralins or mixtures thereof, and the second solvent
25 comprises water and potassium carbonate, and wherein the catalyst is selected from the group consisting of a palladium complex and a nickel complex;

- h) separating the two phases obtained;
- i) recovering 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one;
- j) dissolving the product of step i in acetone;
- 5 k) acidifying the solution;
- l) neutralizing the solution and separating the trityl alcohol, whereby a second solution is obtained;
- m) acidifying the second solution;
- n) cooling the acidified second solution; and
- 10 o) recovering irbesartan.

42. A process for making irbesartan comprising the steps of: reacting an acid addition salt of 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one with 4-bromobenzyl bromide in a two-phase solvent system having a first, organic phase and a second, aqueous phase in the presence of an inorganic base, whereby 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one is obtained, and converting
15 the 2-butyl-3-(4'-bromobenzyl)-1,3-diazaspiro[4.4]non-1-ene-4-one to irbesartan by reacting it with 2-(1-trityl-1H-tetrazol-5-yl)phenylboronic acid and, subsequently, cleaving the trityl group from the tetrazole ring.